REMARKS

Status of the Application

Claims 20-216 remain pending in the present application upon entry of the claim amendments above. Applicants thank the Examiner for her kind consideration in the telephone conferences, the first on December 12, 2002 regarding the revised election of species and the second on May 23, 2003, regarding the outstanding Office Action. Both Interview Summaries accurately reflect the substance of the conferences.

Applicants note for the record that the art-recognized sequence numbering for the beta-subunit of human chorionic gonadotropin is correctly shown in Figure 4, and is now reflected in SEQ ID NO:3. The Sequence Submission that accompanies this Amendment corrects SEQ ID NO:3 to conform with the sequence in Figure 4.

Support for Claims 20-214 is found in Figure 4 of the Specification and in the originally filed claims, as well as at page 73, lines 22-27; page 73, line 28 to page 74 line 2, page 74, lines 3-11, page 74, lines 24-28, page 74, line 29 to page 75, line 3, page 75, lines 4-11, and page 75, lines 18-27. Accordingly, no new matter is incorporated by this Amendment.

Formal Matters

The Sequence Submission that accompanies this Amendment corrects the discrepancy noted with respect to SEQ ID NO:3. Changes to the Specification are made to correct the typographical error noted in the Office Action and for consistency with respect to all references in the Specification noting particular positions or substitutions of the amino acid sequence of the beta-subunit of human chorionic gonadotropin as demonstrated in Figure 4, and SEQ ID NO:3.

Rejection under 35 U.S.C. § 112

Claims 1, 2 and 5-7 are rejected under 35 U.S.C. § 112, second paragraph as purportedly indefinite. The rejection has been rendered moot by the amendments above which have been

entered to more particularly identify the invention. Reconsideration and withdrawal are respectfully requested.

Claims 1, 2 and 5-7 are rejected under 35 U.S.C. § 112, first paragraph as purportedly lacking enablement for those species not rejected for other reasons. The rejection appears to rely on the purported indefiniteness in the claims. In addition, the Office Action correctly stipulates at page 5, lines 2-3, that it would not be undue experimentation to produce each of the species within the scope of the claim. Accordingly, the rejection is rendered moot by the claim amendments above.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 102

The Office Action rejects Claims 1, 2 and 7 under 35 U.S.C. § 102(a) as purportedly anticipated by Moyle, WO 98/58957. The rejection is rendered moot by the claim amendments above.

The Office Action rejects Claims 1, 2 and 7 under 35 U.S.C. § 102(b) as purportedly anticipated by Lund, et al., WO 97/04098. The rejection is rendered moot by the claim amendments above.

The Office Action rejects Claims 1, 2 and 5 under 35 U.S.C. § 102(b) as purportedly anticipated by Campbell, et al., WO 91/16922. The rejection is rendered moot by the claim amendments above.

Reconsideration and withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 103

The Office Action rejects Claims 1, 2, 5 and 7 under 35 U.S.C. § 103(a) as purportedly rendered obvious by Campbell, et al., WO 91/16922 alone or in combination with Boime, et al., U.S. Pat. No. 6,242,580. The rejection is rendered moot by the claim amendments above.

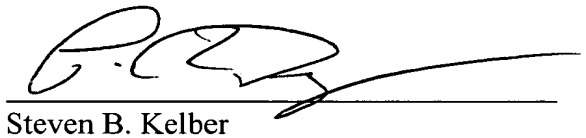
Reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicants respectfully request withdrawal of the rejections. As the claims are otherwise in compliance with the requirements of Title 35, they are in condition for allowance, and notice of the same is respectfully requested. If any points remain in issue that the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



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MARKED-UP COPY OF PARAGRAPHS, AS AMENDED

Replacement for second full paragraph at page 5, line 7 to page 6, line 4:

Compositions and methods based on mutant Cystine Knot Growth Factors (CKGFs) comprising amino acid substitutions relative to the wild type hormone/growth factor. Mutated glycoprotein hormones, including thyroid stimulating hormone (TSH) and chorionic gonadotropin (CG) are disclosed as exemplary mutant CKGFs. Mutant TSH heterodimers and [hCH] hCG heterodimers possessed modified bioactivities, including superagonist activity. Additionally, a variety of mutant CKGF family proteins are disclosed. For example, mutant CKGF proteins disclosed include mutant platelet-derived growth factor (PDGF) family proteins such as mutant PDGF homo- and heterodimers, and mutant vascular epithelial cell growth factor (VEGF) proteins; mutant neurotrophin family proteins such as mutant nerve growth factor (NGF), mutant brain-derived neurotrophic factor (BDNF) proteins, and mutant neurotrophin-3 (NT-3) and mutant neurotrophin-4 (NT-4) proteins; mutant transforming growth factor-ß (TGF-ß) family proteins such as mutant TGF-ß1, mutant TGF-ß2, mutant TGF-ß3, mutant TGF-ß4/ebaf, mutant neurturin, mutant inhibin A, mutant inhibin B, mutant Activin A, mutant Activin B, mutant Activin AB, mutant Müllerian inhibitory substance (MIS), mutant bone morphogenic Protein-2 (BMP-2), mutant bone morphogenic protein-3 (BMP-3)/osteogenin, mutant bone morphogenic protein-3b (BMP-3b), mutant bone morphogenic protein-4 (BMP-4), mutant bone morphogenic protein-5 (BMP-5) (precursor only), mutant bone morphogenic protein-6 (BMP-6)/Vgrl, mutant bone morphogenic protein-7 (BMP-7)/osteogenic protein (OP)-1, mutant bone

morphogenic protein-8 (BMP-8)/osteogenic protein (OP)-2, mutant bone morphogenic protein-10 (BMP-10), mutant bone morphogenic protein-11 (BMP-11), mutant bone morphogenic protein-15 (BMP-15), mutant Norrie Disease protein (NDP), mutant Growth/Differentiation Factor-1 (GDF-1), mutant Growth/Differentiation Factor-5 (GDF-5) (precursor only), mutant Growth/Differentiation Factor-8 (GDF-8), mutant Growth/Differentiation Factor-9 (GDF-9), mutant Glial Cell-Derived Neurotrophic Factor (GDNF)/Artemin, and mutant Glial Cell-Derived Neurotrophic Factor (GDNF)/Persephin proteins. Accordingly, the present invention provides methods for using mutant CKGFs, CKGF analogs, fragments, and derivatives thereof for treating or preventing diseases. Pharmaceutical and diagnostic compositions, methods of using mutant CKGF proteins, including TSH heterodimers and TSH analogs with utility for treatment and prevention of metabolic and reproductive diseases are also provided.

Replacement for fourth full paragraph at page 73 lines 22 to 27:

Introducing acidic amino acid residues where basic residues are present in the hCG beta-subunit monomer sequence is also contemplated. In this embodiment, the variable "X" corresponds to an acidic amino acid. The introduction of these amino acids serves to alter the electrostatic character of the L1 hairpin loops to a more negative state. Examples of such amino acid substitutions include one or more of the following K2Z, [K6Z, K8Z, K10Z] <u>R6Z, R8Z, R10Z</u>, and K20Z, wherein "Z" is an acidic amino acid residue.

Replacement for third full paragraph at page 74, lines 19 to 23:

In another aspect of this embodiment, neutral or acidic amino acid residues in the hCG β subunit, L3 hairpin loop are mutated. The resulting mutated subunits contain at least one mutation in the amino acid sequence of SEQ ID NO: 3 at the following amino acid positions:

N58B, Y59B, D61B, V62B, F64B, E65B, S66B, I67B, L69B, P70B, G71B, P73B, G75B, V76B, N77B, P78B, [G79B] V79B,V80B, S81B,Y82B, A83B,V84B, A85B, L86B, and S87B. "B"is a basic amino acid.

Replacement for fourth full paragraph at page 74, lines 24 to 28:

The invention further contemplates introducing one or more acidic residues into the amino acid sequence of the hCG beta-subunit L3 hairpin loop. For example, one or more acidic amino acids can be introduced in the sequence described above, wherein the variable "X" corresponds to an acidic amino acid. Specific examples of such mutations R60Z, R63Z, R68Z, and [R73Z] R74Z, wherein "Z" is an acidic amino acid residue.